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19 ABSTRACT (Continue on reverse if necessary and identify by block number) <p>This project examined the differential prevalence of a select set of illnesses, including atopic allergies, among first and second degree relatives of children in two cohorts who are high or low in the display of timidity and fear. The rationale for the project was based on the prior finding of a significant difference in atopic allergy between inhibited and uninhibited children, with the former reporting a greater incidence than the latter.</p> <p>A total of 528 relatives in Study 1 and 480 relatives in Study 2 were administered a health interview by telephone. The relatives of the fearful children reported a higher prevalence of hayfever, but not asthma, and the relatives of inhibited children in both samples reported higher levels of social anxiety.</p>					
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## FINAL REPORT

Vulnerability to Allergic Disorder in Families of Children  
of Behavioral Inhibition

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The purpose of this research was to investigate the differential prevalence of physiological and psychological symptoms in the first and second degree relatives of inhibited and uninhibited children, paying special attention to allergic reactions.

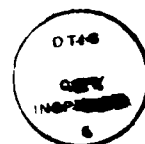
We have now completed the collection and analysis of data from the first and second degree relatives of two cohorts of children. There were 531 adults in one cohort of inhibited and uninhibited children and 468 adults in a second, independent cohort of children who had been assessed for fear at 9, 14, and 21 months of age.

The theoretical basis for this research involves the idea of temperament. The return of the idea of temperament to discussions of personality, after more than a half century of exile, is due to at least three historical factors. The first is ascribable to the influential writings of Thomas and Chess (1) who motivated a generation of scientists to study temperamental phenomena in young children. A second factor is the increased awareness of, and inquiry into, differences in behavior and

biology within, as well as between, related animal species (2,3). Finally, dramatic advances in genetics and the neurosciences have provided initial bases for understanding some forms of behavioral variation in both humans and animals (4,5).

Temperament has become the preferred generic term to refer to the large number of inherited profiles of behavior and biology, present in the infant, that develop into different psychological outcomes depending upon particular histories of childhood experiences. It is not clear how many basic temperamental categories will be discovered, nor how many will prove to be theoretically significant. The number is likely to be larger than the 6 to 10 categories now popular in empirical reports and theoretical essays (6).

Two temperamental categories that have been studied extensively are seen clearly in the second and third years of life. The temperamentally inhibited child consistently displays an initial timidity, shyness, and emotional restraint when exposed to unfamiliar people, places, or contexts, while the uninhibited child approaches the same unfamiliar people and events with minimal uncertainty, often with affective spontaneity (7). A series of reports from our laboratory over the last 12 years reveals that the former group comprises about 10-15 percent of Caucasian children while the latter represents about 20-25 percent of the same population. Further, a majority of the two temperamental types retains their characteristic style of behavior in unfamiliar contexts through the eighth year of life.



Finally, the two groups possess distinctive peripheral, physiological features suggesting that they differ in thresholds of excitability in the limbic system, with the inhibited group having a lower threshold of excitability than the uninhibited group (8).

More relevant to this report is the fact that the mothers of the inhibited, compared with the uninhibited, children, reported a higher prevalence of atopic allergies, especially hayfever and eczema. Although the exact mechanisms mediating this association are not known, recent work in several laboratories has suggested a relation between the central nervous and immune systems that provides some theoretical basis for this result (9).

One such study was an investigation of allergic symptoms in extremely introverted and extraverted college-age adults (10). A total of 375 subjects filled out a self-report scale designed to assess shy behavior. The investigators selected those adults whose scores on the scale fell in the top or bottom 5 percent of the distribution. One-third of the extreme introverts (6 of 18), compared with none of the 19 extraverts, reported having hayfever ( $p < .05$ ). However, the two groups did not differ in the occurrence of asthma or other atopic allergic symptoms. Because there is a genetic contribution to both hayfever (11) and extreme introversion (12), the association between these very different syndromes motivated us to examine the occurrence of a varied set of symptoms in the first and second degree relatives of our longitudinal samples of inhibited and uninhibited children. The

strategy in this study resembles that used by others (13,14).

### Study 1

#### Methods

##### Subjects.

The subjects were 528 first and second degree relatives (parents, grandparents, aunts, and uncles) of 89 Caucasian children who had been selected nine or ten years earlier (when they were either 21 or 31 months of age), because they had been either extremely inhibited or uninhibited when they encountered a wide variety of unfamiliar events in a laboratory setting. The inhibited children were consistently shy, quiet, and timid; the uninhibited children were sociable, talkative, and spontaneous. About 15 percent of the total group of over 400 children had been classified as inhibited and 15 percent as uninhibited, with similar proportions of boys and girls in each group.

The current investigation involved 292 relatives of 48 inhibited children and 236 relatives of 41 uninhibited children. This sample of 89 children represents 83 percent of the original group of 107 children.

Each member of these two temperamental groups was observed on three additional occasions, with the last assessment occurring when the children were 7 1/2 years of age. The initial behavioral differences between the two groups were preserved; the correlations reflecting stability of the individual profile across age ranged between 0.5 and 0.7 (7).

In addition, at every age the inhibited children were more

likely than the uninhibited ones to show signs of high sympathetic tone, as manifested in increases in heart rate across the trials of varied cognitive tests, as well as across the entire one hour battery of procedures, and larger pupillary dilations to cognitive tasks. Inhibited children also showed greater increases in muscle tension in the skeletal muscles of the larynx and vocal cords, higher urinary levels of the derivatives of norepinephrine and higher levels of morning salivary cortisol. An aggregate index of physiological reactivity, based on heart rate, heart rate variability, pupillary dilation, total norepinephrine activity, salivary cortisol, and muscle tension in the vocal cords, was correlated with the index of inhibited behavior at every age of assessment ( $r = .70$  with the original index, and  $.64$  with the index at  $7\frac{1}{2}$  years of age).

#### Procedure

All interviews were conducted by telephone using six different interviewers, none of whom had any knowledge of the psychological characteristics of the child whose relative was being questioned. The interviewer asked the respondents to indicate whether or not they had now or ever had each of 64 medical symptoms, including arthritis, gallstones, back problems, allergies, as well as less frequent symptoms like cancer and rheumatic fever. The interviewer also asked about the occurrence of a select group of psychological characteristics including panic disorder, anxiety disorder, depression, insomnia, and

hospitalization for mental illness.

Finally, the interviewer asked the respondent to indicate, on a five point scale, the degree to which he or she (1) was shy with strangers; (2) liked parties with many people; (3) experienced fear or worry frequently; (4) was shy with peers during childhood; (5) was afraid to go to school during childhood; and (6) experienced heart pounding, blushing, or butterflies in the stomach in the presence of unfamiliar people. The scale scores given to these six separate questions were aggregated (reversing the answer to question number 2 about liking parties) to form an index of social anxiety. A rating of four or five on any of the five point scales was treated as indicative of extreme social anxiety. Any person who provided such an extreme rating on any four of the six questions was classified as socially anxious.

The analyses of the data were straightforward. We compared the two temperamental groups with respect to the frequency of each symptom in the adult relatives. It should be noted that the relatives lived in all regions of the United States and many were not in regular contact with the target child. Therefore, there is little possibility of contamination of these results through conversations about the target child among the geographically scattered relatives.

### Results

As might be expected, there were no significant differences between the two groups of relatives for the vast majority of

symptoms. However, the relatives of the two groups did differ in a small number of symptoms that are in partial accord with prior expectation. As Table 1 reveals, more relatives of inhibited, compared with uninhibited, children reported having hayfever, eczema, and frequent stomach cramps; and, among female relatives, more frequent menstrual problems (amenhorrea or painful, prolonged menstrual cycles). The incidence of hayfever and eczema in the relatives of uninhibited children was close to national norms (11). Further, 61 percent of the inhibited children had at least one relative with eczema compared with 37 percent of the uninhibited children (chi square = 5.5,  $p < .01$ ). It is of interest that the two groups did not differ significantly in the occurrence of asthma or allergic reactions to food or medicine. This result is in accord with the prior study on college students where hayfever was the only allergic symptom that differentiated the extreme introverts from the extreme extraverts.

TABLE 1 HERE

Two other symptoms produced differences between the two groups that, after the fact, are theoretically reasonable, although both missed conventional levels of statistical significance. More parents of inhibited children reported gastric or peptic ulcers (8 versus 0 percent), and a psychiatric diagnosis of anxiety disorder (8 versus 4 percent). It is not the case that the relatives of inhibited children simply answered affirmatively more often because the relatives of uninhibited



children reported higher frequencies for some symptoms (e.g., arthritis or diabetes).

The self-ratings on the six social anxiety questions revealed that more relatives of inhibited than uninhibited children answered at least four of the six questions with a rating of four or five, which is indicative of high social anxiety (9 versus 5 percent,  $p < .005$ ). Additionally, the mean self-rating across all six questions were significantly higher for the relatives of inhibited compared with uninhibited children ( $t = 3.69$ ;  $p < .001$ ).

#### Study 2.

A second longitudinal cohort that is being followed in our laboratory provided an opportunity for a partial replication of the results of Study 1. We are studying a volunteer sample of healthy, Caucasian infants born to middle class mothers in order to discover the infant characteristics that might predict the display of inhibited or uninhibited behavior in the second year. These infants varied in display of fearful behavior at 14 months of age and we conducted the same interview with the first and second degree relatives of these children.

#### Methods

##### Subjects.

The subjects were 480 first and second degree relatives of 59 infants (116 parents, 91 aunts, 96 uncles, and 177 grandparents). The 59 infants were born to middle class mothers who reported no excessive consumption of alcohol, coffee, or

tobacco during their pregnancies and all infants were term births with no pre- or perinatal complications.

### Procedures

Adult Interview. The adults were administered by telephone the same questionnaire used in Study 1 by interviewers who had no knowledge of the psychological characteristics of the child.

Procedures with the Infants. At four months of age the infants were evaluated with a 45 minute laboratory battery designed to assess their responsivity to visual, auditory and olfactory stimulation. The two primary variables quantified were motor activity and crying to the unfamiliar stimuli. The decision to code these variables was based on the assumption that variation in limb movement and fretting/crying to unfamiliar stimulus events reflected thresholds of arousal in limbic sites, especially the amygdala and its projections to the corpus striatum and central grey. Fifteen of the 59 infants were classified as displaying high motor activity and frequent crying while 20 infants displayed low motor activity and infrequent crying. Twenty-four of the infants showed a mixed profile of either high motor with infrequent crying or low motor with frequent crying (see 15 for details).

All infants were assessed in the laboratory when they were 14 months old for fearful behavior to a variety of unfamiliar events. The situations designed to elicit fear included the placement of electrodes on the child for the recording of heart rate, a rotating wheel containing colored objects that produced

noisy stimulation, application of a blood pressure cuff, requests by an examiner to imitate acts that were unfamiliar (putting a finger into a cup of black liquid), requests to taste liquid from an eye dropper, the examiner speaking a nonsense phrase in a stern voice with a stern face while presenting an attractive rotating toy, invitation by a stranger to approach and play with her toy, and an invitation by an unfamiliar woman to approach a metal robot. Fear in these situations was defined as fretting or crying to any of the unfamiliar events or failure to approach the stranger or the robot despite an invitation to do so.

A total of 19 of the 59 infants displayed low fear across all the incentives (zero or one fear); 20 percent showed moderate fear (two or three fears); and 20 infants showed high fear (four or more fears). When we combined these fear scores at 14 months with the motor activity and cry scores displayed at four months, there were 14 children who showed both high motor activity and frequent crying at four months as well as moderate or high fear at 14 months and 12 children who showed low motor activity and infrequent crying at four months together with low fear at 14 months. The former group is regarded as temperamentally inhibited; the latter group as temperamentally uninhibited.

### Results

As in Study 1, there were no differences between the first and second degree relatives of the temperamentally inhibited and uninhibited groups for the vast majority of symptoms. The only difference between the two groups in occurrence of atopic allergy

reactions involved hayfever in the parents. Thirty-two percent of the parents of the temperamentally inhibited children reported having hayfever compared with 14 percent of the uninhibited children ( $p < .05$ ). Further, 64 percent of the inhibited children, compared with 25 percent of the uninhibited children, had at least one parent with hayfever ( $p < .05$ ). The occurrence of eczema, cramps, and menstrual problems did not differentiate the two groups. It is of interest that 14 percent of the grandparents of the temperamentally inhibited group reported cancer of the gastrointestinal tract, blood, uterus, breast, or prostate, compared with 3 percent of the grandparents of the uninhibited group,  $p < .05$ .

As in study 1, significantly more relatives of the temperamentally inhibited children had high social anxiety scores (11 versus 1 percent,  $p < .01$ ). Further, 69 percent of the temperamentally inhibited children had at least one relative who admitted to high social anxiety, compared with 11 percent of the uninhibited children ( $p < .01$ ). Three inhibited children, but not one uninhibited child, had at least one relative who reported a psychiatric diagnosis of anxiety disorder.

#### Relations Among the Symptoms

We examined the degree of association, for each sample separately, among the small number of symptoms that, a priori, might have differentiated the temperamental groups (respiratory and skin allergies, asthma, ulcers, gastritis, colitis, migraine, anxiety disorder, and extreme social anxiety). These analyses

were performed within sex for the relatives of the inhibited and uninhibited children separately.

Most of the associations were not consistent across the eight groups of subjects (sample by sex by temperament). However, some associations were more consistent than others. The occurrence of eczema was associated with the occurrence of hayfever for three of the four subgroups in sample 1 ( $p < .05$ ), and, in sample 2, skin allergies were associated with hayfever for two of the four groups. High social anxiety was associated with occurrence of either skin or respiratory allergies for all eight groups.

Table 2 provides a summary of the significant relations among the symptom classes for each of the eight groups. Symptoms of the gastrointestinal tract (ulcers, colitis, gastritis) were associated with allergic symptoms in five of the eight groups. Reports of skin or respiratory allergies were associated with migraine headaches for all four groups of women, with social anxiety for three of the four groups of women, and with symptoms of the gastrointestinal tract for three of the four groups of men and two of the four female groups. Further, symptoms of the gastrointestinal tract were associated with social anxiety for three of the four female groups.

In general, the association among atopic allergies and social anxiety was stronger for women than for men. For example, among 156 female relatives of inhibited children in sample 1, 15 reported having asthma (9 percent), 15 (9 percent) reported being

extremely shy and 6 women reported both symptoms ( $p < .001$  by the Exact Test). Among 127 female relatives of uninhibited children in sample 1, 28 reported a skin allergy (22 percent); 8 reported anxiety disorder (6 percent), and 5 reported both symptoms ( $p < .05$  by the Exact Test). These data lend support to the idea of an association between social anxiety, on the one hand, and respiratory allergy and gastrointestinal symptoms, on the other, especially among women.

### Discussion

The data suggest that the first and second degree relatives of young children who were extremely shy, timid, and fearful admit to high levels of social anxiety. This result is in accord with reports in the psychiatric literature suggesting that social anxiety runs in families and that introversion-extraversion is a heritable trait (4, 12).

The novel evidence in this report is the possible association between extreme degrees of shy, fearful, behavior in children and the occurrence of hayfever in their relatives. This association occurred for the parents in Study 2 and for all first and second degree relatives in Study 1. The bases for this association are unclear.

Many neurochemical mediators whose levels rise both in the nasal allergic secretions and the plasma of allergic rhinitis patients during allergic reactions are also active in the limbic system as neurotransmitters or neuromodulators that affect emotional mood (16, 17, 18). The response of the olfactory

epithelium to many forms of stimulation, including allergens, is modulated by sympathetic and parasympathetic nervous system (19). The inhibited children in both Study 1 and Study 2 are characterized by high reactivity of the sympathetic nervous system, as reflected in large cardiac accelerations and pupillary dilations to cognitive stress and physical challenge (for example, sour tastes) and larger increases in diastolic blood pressure to orthostatic challenge). Thus, it is possible that the association reported here is being mediated, in part, by physiological factors related to sympathetic reactivity.

It is also possible that activity in the pituitary-adrenocortical axis is relevant to this association for glucocorticoids affect the immune system (20) and more uninhibited than inhibited children have very low salivary cortisol levels (7).

In sum, the evidence is in accord with the suggestion that the complex genetic factors that participate in the mediation of extreme degrees of shy, timid behavior in children and introversion in adults are correlated, or perhaps identical, with those factors that influence immunological vulnerability to selected atopic allergies. This intriguing relation invites future exploration.

TABLE 1  
Proportion of Relatives of Inhibited and Uninhibited Children  
Reporting the Occurrence of Selected Symptoms in Study 1

<u>Symptoms</u>	<u>Inhibited</u> (N = 292)	<u>Uninhibited</u> (N = 236)	<u>Probability</u> (Exact Test)
Hayfever	32	23	< .01
Eczema	18	8	< .01
Stomach Cramps	11	6	< .05
Menstrual Problems	26	14	< .05
High Social Anxiety	9	5	< .005



Table 2  
Significant Association Among Four Classes of Symptoms  
In Eight Groups of Relatives

<u>Associated Symptoms</u>	<u>Sample 1</u>		<u>Sample 2</u>	
	I	NI	I	NI
Allergy/Gastrointestinal	M F	M	F	M
Allergy/Migraine	F	F	F	F
Allergy/Anxiety	M F	F		F
Gastrointestinal/Migraine				
Gastrointestinal/Anxiety	F		F	F
Migraine/Anxiety				

M = Male relatives

F = Female relatives

I = Relatives of inhibited children

NI = Relatives of uninhibited children

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Publications and Reports

Bell, I. R., Jasnoski, M. L., Kagan, J., and Keane, D. S., Is allergic rhinitis more frequent in young adults with extreme shyness?, Psychosomatic Medicine (in press).

Kagan, J., Snidman, N., Sellers, M. J., and Johnson, M. O., Temperament and Allergic Symptoms (submitted to Psychosomatic Medicine).

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Student Employees:

Graduate Students:              Female (5)

Postdoctoral Fellows:          Female (2), Hispanic (1).